

## **II. REMARKS**

### **Preliminary Remarks**

This response is being timely filed, as it is being filed with a petition for a one-month extension of time and the requisite fee. After entry of this amendment, claims 1-13 and 18-24 will be pending in this application, with claims 3-8, 19, 21, and 22 having been withdrawn from consideration pursuant to a previous restriction requirement. In this response, the applicants have amended claims 1-9, 12-13, and 18-24. The particular amendments to the claims will be described below in more detail. No new matter is believed to have been introduced by any of the amendments.

### **Request for Acknowledgement of Priority**

This application is the national stage of PCT/GB99/03258, filed October 1, 1999, which claims priority to GB 9821393.7, filed October 1, 1998. The specific reference required by 37 C.F.R. § 1.78 was inserted as the first sentence of the application by the instructions in #11 of the transmittal letter filed with the application on March 30, 2001. However, none of the official actions from the examiner have acknowledged the claim to priority, or have given any indication as to whether the certified copies have been properly transmitted from the international bureau. **Accordingly, the applicants respectfully request an acknowledgement of priority in the next official action, along with an indication that the certified copies have been received from the international bureau.** (The applicants note that the Notification of Acceptance mailed August 2, 2001 indicates that the priority document was received.)

### **Comments on the Restriction Requirement**

The applicants appreciate the examiner's detailed comments on the matter of the restriction requirement and his willingness to re-examine the issues as the prosecution of this application proceeds. However, as a formal matter, the applicants respectfully submit that the restriction requirement is improper and, accordingly, request that it be withdrawn. Specifically, this application is the national stage of a PCT application; therefore, **it is the unity of invention rules under 37 C.F.R. § 1.475 and 1.499 that apply to this application, not the restriction practice under 37 C.F.R. §§ 1.141 – 1.146, which applies only to applications filed under 35 U.S.C. § 111(a).**

To the extent that the applicants responded to the improper restriction requirement set forth in the previous official action, some clarification appears to be in order. The applicants' primary argument was that it would not be a burden to search and examine all of the claims. As MPEP § 803 states, "if the search and examination of the entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions." The applicants believe that that policy should apply to the present application, in order to prevent both delay and the undeniable burden of duplicative examination. The applicants make no statement or admission as to the relative patentability of one group of claims over another, and repudiate any admission that might be inferred from the record to date.

Furthermore, the applicants believe that the various independent claims have a common special technical feature, which would make their restriction under unity of invention practice improper.

In order to facilitate the consideration of the (improperly) withdrawn claims, the applicants have taken this opportunity to amend them along with the other claims.

#### Claim Objection

Claims 9-13, 18, and 20 were the subject of an objection under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. The applicants have amended those claims appropriately to correct their dependencies. Accordingly, the applicants submit that the objection has been overcome and request that it be withdrawn.

#### Patentability Remarks

##### 35 U.S.C. § 112

Claims 9-13, 18, and 20 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite because of their dependencies. As was noted above, the applicants have now amended those claims to correct their dependencies. Accordingly, the applicants respectfully request that the rejection be withdrawn.

##### 35 U.S.C. § 103

The claims of the present application were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over a number of different references, each taken individually.

Because of the nature of the rejections, and the apparently common reasoning behind them, the applicants will address the rejections *en masse* before delving into the particular teachings of any one reference or the propriety of any one rejection.

Specifically, claims 1, 2, and 23 were rejected over Tarr, U.S. Patent No. 5,824,556 (hereinafter “the ‘556 patent”). Claims 1, 2, 9, 13, 18, and 23 were rejected over Hutchens, U.S. Patent No. 6,124,137 (hereinafter “the ‘137 patent”). Those same claims were also rejected over Laal, U.S. Patent No. 6,245,331 (hereinafter “the ‘331 patent”). Additionally, claims 1, 2, 18, and 23 were rejected over Furuya, 163 *Biochem Res. Commun.* 1100 (1989) and over Korostensky, 19 *Electrophoresis* 1933 (1998).

The list of references applied by the examiner is lengthy and diverse, to say the least. The examiner’s position appears to be based on four major assertions, which the applicants enumerate for convenience and will address in turn. In particular, the examiner asserts that:

- (1) the claims do not require the method steps to be performed in order;
- (2) the “isolation” steps recited in the claims do not explicitly require separation;
- (3) any cleaved peptide will necessarily contain the C-terminus or N-terminus of the peptide from which it was fragmented;
- (4) the first cleavage agent recited in certain of the claims is not explicitly required to be different from the second cleavage agent recited in the claims, only the actual cleavage site is required to be different.

Based on those four assertions, the examiner embarks on a wholesale reordering, broadening, and re-interpretation of the claims. The extent of the examiner’s efforts to make the references read on the claims is evident from the International Preliminary Examination Report, which found that claims 1-17 satisfied the requirements for novelty, inventive step, and industrial applicability after considering some of the same documents.

The applicants understand that the examiner’s duty is to give the claims their “broadest reasonable interpretation,” but submit that that interpretation must be “consistent with the specification.” See, for example, MPEP § 2111, citing *In re Hyatt*, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Although the applicants have made certain amendments to the claims to render some of the examiner’s assertions moot, the applicants submit that, especially in certain cases, the examiner’s interpretation of claim terms is clearly not consistent with the specification.

For example, the applicants submit that the examiner’s assertion that the recited “isolation” step does not explicitly require separation is not consistent with the specification

or with the ordinary meaning of that term. As described in the specification on page 15, lines 16 to 20, and page 19, lines 14-28, “isolation” inherently encompasses the separation of the polypeptide fragments from the cleavage reaction mixture.

Moreover, with respect to assertion (3), the claims have always distinguished between “polypeptides” present in the original sample and the “polypeptide fragments” created by the cleavage steps. Therefore, under any reasonable claim construction, it is clear that the fragments comprise the N- or C- terminus of a polypeptide present in the original population of polypeptides to be characterized. However, the applicants have amended independent claims 1, 5, 21, and 23 to recite that each polypeptide fragment contains either the N-terminus or C-terminus of the parent polypeptide from which the polypeptide fragment was fragmented. The applicants believe that this amendment renders the examiner’s assertion moot, and do not view the amendment itself as narrowing.

With respect to assertions (1) and (4), the applicants have amended the claims to recite first and second portions of the sample, respectively, that are separate from one another, and to recite that the first cleavage agent is different from the second cleavage agent. These amendments emphasize that the two portions of the sample may be treated separately in parallel reactions, and are believed to render assertions (1) and (4) moot.

In addition to the amendments made in response to one or more of the examiner’s assertions, the applicants have made a number of typographical corrections to claims 18-24.

As to the individual rejections, the ‘556 patent discloses a method of sequencing a peptide by chemically generating a number of N-terminally truncated peptides for mass spectrometry. The method of the ‘556 patent comprises sequentially cleaving the N-terminal amino acid using carbon disulphide and an acid. However, each cleavage step of the ‘556 patent is applied to the same aliquot of sample, which gives rise to a series of reaction cycles, *i.e.*, each subsequent cleavage step takes place on the product of the previous cleavage step. The ‘556 patent does not disclose a separate isolation task. The examiner has essentially admitted all of this in making the rejection, and in the discussion that gave rise to the four assertions set forth above.

As amended, independent claims 1 and 23 recite first and second separate portions of the sample, and first and second sequence-specific cleavage agents that are different from one another. The applicants submit that there is no disclosure or suggestion of a method having such features in the ‘556 patent. Moreover, dependent claim 2 is not obvious over the ‘556

patent for at least the same reasons as claim 1, from which it depends. Accordingly, the applicants respectfully request that the rejection be withdrawn.

The '137 patent discloses a system for presenting an analyte to an energy source for desorption and subsequent detection by, for example, mass spectroscopy. The system comprises a probe having a surface for presenting an analyte to an energy source that emits energy capable of desorbing the analyte from the probe surface, and a layer of energy absorbing materials which are capable of absorbing the energy and enabling desorption of the analyte.

In making the rejection, the examiner refers to column 35, lines 54-65 of the '137 patent. However, in contrast to independent claims 1 and 23, that passage of the '137 patent describes a method in which reagents are sequentially applied to a single aliquot of the same sample in a series of reaction cycles. There is no disclosure or suggestion of the first and second separate sample portions or the separate isolation steps that are recited in claims 1 and 23. Moreover, the applicants note that carboxypepsidase-Y is a non-sequence-specific cleavage reagent, whereas claims 1 and 23 recite that the first and second cleavage reagents are sequence-specific. Accordingly, the applicants submit that independent claims 1 and 23, and the claims that depend from them, are not obvious over the '137 patent, and respectfully request that the rejection be withdrawn.

The '331 patent relates to a method of detecting active mycobacterial disease. The examiner refers specifically to column 42, lines 10-38, which describe subtilisin and chymotrypsin/trypsin digestions of a 45 kDa glycoprotein for mass spectroscopy. However, there is no disclosure or suggestion of "isolating one or more polypeptide fragments, each fragment comprising the N-terminus or the C-terminus of the parent polypeptide from which it was fragmented" from the aliquot, as is recited in independent claims 1 and 23, nor does the '331 patent offer any disclosure or suggestion of a method for characterizing a population of polypeptides, as those claims recite. Accordingly, the applicants respectfully submit that independent claims 1 and 23, and the claims that depend from them, are not obvious over the '331 patent, and request that the rejection be withdrawn.

The Furuya article discloses the digestion of EGF separately with chymotrypsin, thermolysin, and trypsin, and the analysis of the resulting fragments using mass spectroscopy. However, there is no disclosure or suggestion of isolating a peptide fragment from the N-terminus or C-terminus of the parent polypeptide, and there is no disclosure or suggestion in the Furuya article of a method of characterizing a population of polypeptides, as recited in

independent claims 1 and 23. Accordingly, the applicants respectfully submit that independent claims 1 and 23, and the claims that depend from them, are not obvious over the Furuya article, and request that the rejection be withdrawn.

The Korostensky article discloses methods for the identification of proteins using peptides with ragged N- or C- termini generated by sequential endo- and exopeptidase digestions. The examiner cites column 2, paragraph 2, which relates to the cleavage of a protein with an endopeptidase followed by cleavage of the resulting fragments with an exopeptidase that cuts amino acids from either the C- or N-terminus. However, it is clear from the description that each cleavage step is applied to the same portion or aliquot of the sample, giving rise to a series of reaction cycles. There is no disclosure or suggestion in the Korostensky article that cleavage steps be performed on separate portions of the sample, nor is there any disclosure or suggestion that the polypeptide fragments be isolated, all of which are recited in independent claims 1 and 23. Moreover, there is no disclosure or suggestion of a method of characterizing a population of polypeptides. Accordingly, the applicants respectfully submit that independent claims 1 and 23, and the claims that depend from them, are not obvious over the Korostensky article, and request that the rejection be withdrawn.

**III. CONCLUSION**

In view of the foregoing, the applicants respectfully submit that this application is in condition for allowance. A timely notice to that effect is respectfully requested. If any questions remain, the examiner is encouraged to contact the undersigned.

Respectfully submitted,

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